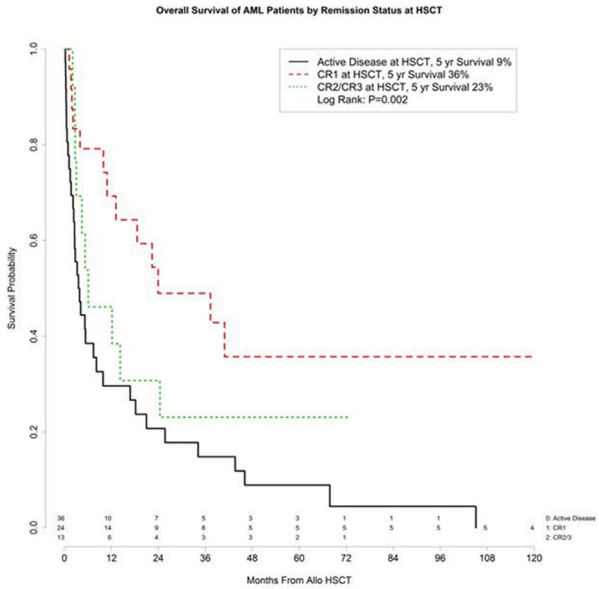

Figure 2. Overall Survival of AML Patients by Remission Status.

Median times to neutrophil and platelet engraftment were 17 and 19 days, respectively. Grade 3-4 aGVHD occurred in 20% and 14% in the total cohort and AML subset respectively. cGVHD developed in 54% (17% extensive stage) and 35% (8% extensive stage) of pts in the total cohort and AML subset respectively.

The 5 year OS for the entire cohort was 29% [95% CI (23%-36%)], and varied by diagnosis (Fig 1). NRM at 100 days was 17% [95% CI (13%-23%)].

On univariate analysis of the entire cohort, only 1-antigen mismatch [HR 1.96, p-value=0.01] and KPS <80 [HR 10.66, p-value <0.001] were associated with worse OS. In the AML cohort, active disease at HSCT (HR 2.43 p=0.001), failure to engraft (HR 4.84 p<0.001), and grade 3-4 aGVHD (4.08 p<0.001) were associated with worse OS. In multivariate analysis after stepwise selection, advanced age (aHR 1.36, p=0.04), active disease (aHR 2.46, p-value=0.003) (Fig 2), engraftment syndrome (aHR 43, p=0.001) and grade 3-4 aGVHD (aHR 5.23 p<0.001) were associated with worse OS.

Conclusions: We report over a decade of experience with the PPT regimen. OS and low NRM are similar to other reported RIC regimens despite high rates of active disease at HSCT. Rates of severe acute and extensive chronic GVHD were low. PPT remains a viable regimen for pts not eligible for myeloablative conditioning.

15

Killer Immunoglobulin-like Receptor (KIR) Genotypes Influences NK Cells' Response to Epstein - Barr Virus and the Risk of Developing Post-Transplant Lymphoproliferative Disease (PTLD) after Allogeneic HCT

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Background: A compromised immune system of Hematopoietic Cell Transplantation (HCT) recipients early after transplantation renders them vulnerable to a heightened risk of reactivation of otherwise latent viral infections. Uncontrolled reactivation of Epstein-Barr virus (EBV) is one of such events that can culminate into post-transplant lymphoproliferative disorder (PTLD), a complication associated with high risk of mortality. Recovering within weeks after transplantation and being first in the line of defense against viral infections, natural killer (NK) cells are deemed important in the immune surveillance against the reactivation and complications of EBV. Their role however remains elusive. The complexity of NK cell response is a function of a series of activating and inhibitory cell surface receptors known as Killer Immunoglobulin-like Receptors (KIR), which sense perturbations in HLA expression after viral transformation of the target cell. Here, we set out to determine whether and how KIR gene repertoire of HCT donors and/or recipients influences the development of PTLD after allo-HCT.

Study Design: KIR gene repertoires of 356 HLA-matched donor-recipient pairs of first allo-HCT and 50 healthy individuals were determined by Luminex based rSSO method. The KIR genotypes were classified into AA and B/x genotypes. Presence or absence of one or more haplotype-B defining KIR genes further identified genotypes for centromeric (Cen) and telomeric (Tel) parts of the KIR locus. PBMNCs from 50 KIR-genotyped healthy volunteers were stimulated with EBV-transformed cells to enumerate EBV-induced NK cell response (degranulation and/or IFNγ production) as a function of KIR gene distribution using a multicolor flow cytometry-based assay. Effect of KIR gene repertoires on development of PTLD was analyzed using binomial competing risks regression statistics.

Results: Donor telomeric A motifs (Tel-A, KIR3DL1^{+ve}-KIR2DS4^{+ve}; KIR3DS1/2DS1$^{+/-ve}$), strongly protected against PTLD (p=0.0002, SHR=0.21; Figure 1A). The protection of donor Tel-A motifs against PTLD shows a dose dependent effect as cumulative incidence of PTLD in HCT recipients receiving graft from donors carrying two Tel-A motifs, one Tel-A motif and no Tel-A motif was 6%, 11% and 19% respectively. Further, the numbers of EBV induced functional NK cell subsets were significantly higher in individuals with than without KIR genotypes containing Tel-A motifs (Figure 1B).

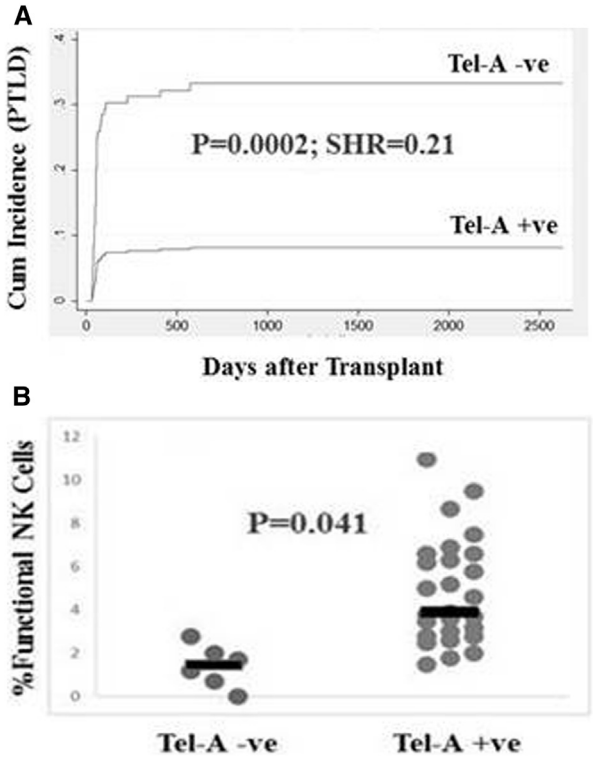

Figure 1. Influence of KIR Telomeric-A (Tel-A) motifs on [A] the development of PTLD after allogeneic HCT; and [B] NK cell response against EBV transformed cells.

Conclusions: NK cell responsiveness, a function of KIR gene repertoire has a profound effect on the development of PTLD. KIR genotype based identification of HCT donor-recipient pairs at high risk of developing PTLD will enable closer monitoring of EBV DNAemia and facilitate prompt therapy.

16

Outcomes of Second Unrelated Donor Cord Blood Transplants (UCBT) Performed in Children with Graft Failure of Autologous Recovery Following the First UCBT

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Background: In the past 20 years, use of UCBT has improved access to transplantation, particularly in children and ethnic minorities. Rapid donor availability, partial HLA matching and low incidence of graft versus host disease (GVHD) are important advantages. UCBT outcomes have significantly improved in the last decade due to better graft availability and donor selection. However, a small fraction of recipients develop auto-recovery or graft failure and are candidates for a second transplant. In most cases, due to urgency and original limitations in donor choices, another cord blood unit (CBU) is the best option for these children.

Table
Characteristics of 2nd UCBT

Characteristics of 2nd UCBT		
Gender	**N**	**%**
Male	30	83.3
Primary Disease		
Heme malignancy	16	44.4
Inherited metabolic disease	10	27.8
Marrow failure	4	11.1
Immunodeficiency	3	8.3
Hemoglobinopathy	3	8.3
Reason for 2nd UCBT		
Primary graft failure	25	69.4
Late graft failure	3	8.33
Autologous recovery	8	22.2
Demographics	**median**	**range**
Age at 2nd UCBT (years)	7.4	1.5-20.9
Weight at 2nd UCBT (kg)	22.9	9.0-108.0
Time from 1st to 2nd UCBT (days)	61.5	42-3454
Cell Dose (n=39)		
Cryopreserved TNCs x 10^7/kg	5.6	1.3-21.9
Reinfused TNCs x 10^7/kg	4.6	1.1-18.1
Reinfused $CD34^+$ x 10^5/kg	1.4	0.1-15.0
Reinfused $CD3^+$ x 10^6/kg	9.1	1.5-34.4
Reinfused CFUs x 10^4/kg	5.7	0.0-175.4

Methods: Retrospective analysis of all pediatric patients (<21 years) undergoing UCBT at Duke between 1995 and 2013 who subsequently received a second UCBT due to graft failure or auto-recovery after the first UCBT (n=36) was conducted. Patients requiring second transplants for relapse were excluded. Kaplan-Meier estimates of overall survival (OS) and cumulative incidence (CI) of engraftment and GVHD were calculated. All received reduced intensity conditioning for the second transplant. The most common prep regimen was cyclophosphamide 60mg/kg x 2 and equine ATG 30mg/kg x 3 (n=15). Single cord (n=28), double cord (n=3) or cord +haplo graft (n=5) were the donor sources. Demographic, disease and graft characteristics are shown in the Table.

Results: The OS at 100 days, 1 year and 5 years was 50.0%, 37.1% and 33.3% respectively. Mortality was lower for patients transplanted after 2007, but the difference was not statistically significant (p=0.33) (see Figure). Median time to neutrophil (ANC 500) and platelet (50K) engraftments were 27 (range, 12-94) and 98 days (range, 37-434) respectively. The probability of neutrophil engraftment at day 42 was 64.3%. The CI of grades II-IV and grades III-IV acute GVHD, at 100 days was 47.1% and 31.3% respectively. Extensive/chronic GVHD was seen in 3 patients (CI=13.6%).

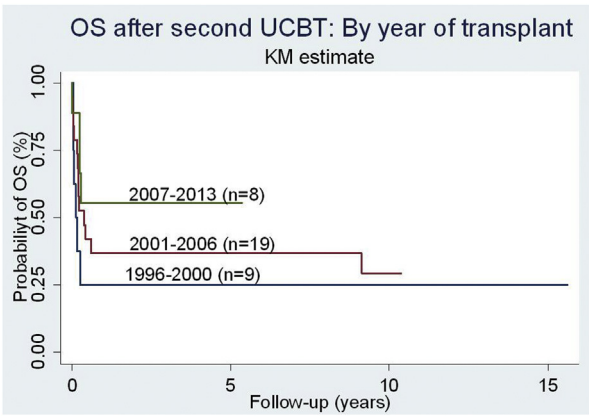

Figure.